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Standard Guide for Stability Testing of Cannabis-Based Products[1]

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1. Scope

1.1 This guide is applicable to commercial processors and manufacturers engaged in the processing, testing, packaging, labeling, and storage of cannabis products intended for human consumption, including those derived from hemp. Hemp seed and products derived from hemp seed are excluded from the scope of this guide This guide describes the minimum requirements for conducting stability testing of new cannabis products with the purpose of determining appropriate storage conditions and shelf-life.

1.2 This guide applies to all cannabis-derived products commercially manufactured and distributed for consumer use, regardless of the type of cannabis plant from which they were derived.

1.3 *Units*—The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.4 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.5 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

D8270 Terminology Relating to Cannabis

D8282 Practice for Laboratory Test Method Validation and Method Development

2.2 *ICH Documents:*[3]

Q1A(R2) Harmonised Tripartite Guideline – Stability Testing of New Drug Substances and Products

Q1B Harmonised Tripartite Guideline – Stability Testing: Photostability Testing of New Drug Substances and Products

3. Terminology

3.1 *Definitions:*

3.1.1 For definitions of terms, see Terminology D8270.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *accelerated testing, n*—studies designed to increase the rate of chemical degradation or physical change of a product by using exaggerated storage conditions as part of the formal stability studies.

3.2.1.1 *Discussion*—Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions (for example, during shipping). Results from accelerated testing studies are not always predictive of physical changes.

3.2.2 *cannabis product, n*—products derived from the cannabis plant (flowers or resins) that are intended for human consumption and are packaged and labeled in their final form for marketing.

3.2.3 *climatic zones, n*—the four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions.

3.2.3.1 *Discussion*—Zone 1 is temperate, Zone II is subtropical, Zone III is hot dry, and Zone IV is hot humid/tropical. This is based on the concept described by Grimm, 1985 and 1986.[4]

3.2.4 *D65/ID65, n*—an illuminant standard used to represent daylight as defined by the International Commission on Illumination.

[1] This guide is under the jurisdiction of ASTM Committee D37 on Cannabis and is the direct responsibility of Subcommittee D37.03 on Laboratory.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Secretariat, Route de Pré-Bois, 20, P.O Box 1894, 1215 Geneva, Switzerland, https://www.ich.org.

[4] Grimm, W., *Drugs Made in Germany*, Vol 28, pp. 196–202, 1985, and Vol 29, pp. 39–47, 1986.

3.2.4.1 *Discussion*—ID65 is the indoor equivalent of the D65 standard.[5]

3.2.5 *expiration date, n*—the date placed on the packaging or label, or both, that displays the time period during which the product is known to remain stable, which means it retains its strength, quality, and purity when it is stored according to its labeled storage conditions.

3.2.6 *extrapolation, n*—the practice of using a known data set to estimate information about future data.

3.2.7 *long-term testing, n*—stability studies under the recommended storage condition for the re-test period or shelf-life proposed (or approved) for labeling.

3.2.8 *mass balance, n*—the process of adding together the assay value and levels of degradation products to see how closely these add up to 100 % of the initial value, with due consideration of the margin of analytical error.

3.2.9 *shelf-life, n*—(also referred to as *expiration dating period*)—the time period during which a cannabis product is known to remain within the final product specifications, provided that it is stored under the conditions defined on the container packaging or label, or both.

3.2.10 *storage condition tolerances, n*—the acceptable variations in temperature and relative humidity of storage facilities for formal stability studies.

3.2.10.1 *Discussion*—The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity must be monitored, documented, and controlled throughout the stability study. Short term temperature/humidity excursions that occur due to opening doors of the storage chamber are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

3.2.11 *stress testing, n*—studies undertaken to elucidate the intrinsic stability of the cannabis products.

3.2.11.1 *Discussion*—Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

3.2.12 *supporting data, n*—data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf-life, and the label storage statements.

3.2.12.1 *Discussion*—Such data include (*1*) stability data on early small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (*2*) information regarding test results on containers; and (*3*) other scientific rationales.

[5] International Commission on Illumination (CIE) and International Organization for Standardization (IS) joint standard, *Colorimetry – Part 2: CIE Standard Illuminants for Colorimetry*, CIE S 014-2/E:2006/ISO 11664-2:2007(E).

4. Significance and Use

4.1 Stability testing provides evidence on how the quality and safety of cannabis-based product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. The stability testing will also establish a re-test period for the cannabis product or a shelf-life for the cannabis product under recommended storage conditions. Recommended test conditions are based on ICH Q1A.

4.2 The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the European Commission (EC), Japan and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV.

4.3 Requirements of regulatory bodies or governmental departments supersede the recommendations in this guide.

5. Stability of Cannabis-Based Products

5.1 Information on the stability of the analyte(s) in cannabis products is an integral part of the systematic approach to stability evaluation.

5.2 *Stress Testing:*

5.2.1 Stress testing of the cannabis-based products can help identify the likely degradation products of analytes contained in the cannabis products, which can in turn help establish the degradation pathways and the intrinsic stability of the analytes and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual analyte(s) and the type of cannabis product involved.

5.2.2 Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

5.2.3 Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

5.3 *Evaluation:*

5.3.1 The purpose of the stability study is to establish a stability timeline, based on the recommendation to test a minimum of three batches of the cannabis product, and to evaluate the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests). A statistical approach should be used to determine the sample size for each batch.

6. Stability Study Design

6.1 The design of the formal stability studies for the cannabis product should be based on knowledge of the behavior, properties of the cannabis product analytes, and from stability studies on those chemicals and on experience gained from formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

6.2 *Photostability Testing:*

6.2.1 Photostability testing should be conducted on at least one initial production batch of the cannabis product if appropriate.

6.2.2 Light sources that meet the D65/ID65 standard for outdoor daylight and indoor indirect daylight may be used for photostability testing. Appropriate control of temperature should be maintained to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. The manufacturer may rely on the spectral distribution specification of the light source manufacturer.

6.2.3 Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts, such as cooling and/or placing the samples in sealed containers, should be made to ensure that the effects, such as sublimation, evaporation, or melting, that result in changes to physical state are minimized.

6.2.4 At the end of the exposure period, the samples should be examined for any changes in physical properties (for example, organoleptic, appearance, clarity or color of solution, separation, odor, etc.) and for assay (refer to Table 1) and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

6.2.5 When powder samples are involved, sampling should ensure that a representative portion of the batch is used in individual tests by using a statistical approach. For solid oral dosage form products such as tablets, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (for example, creams, ointments, suspensions, etc.). The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

6.2.6 The analytical procedures used should be validated prior to testing of stability samples and in accordance with Practice D8282.

6.2.7 Depending on the extent of change, special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order to assure that the product will be within proposed specifications during the shelf-life.

6.3 *Selection of Batches:*

6.3.1 Stability studies should be performed on at least three initial production batches of the cannabis product. The initial production batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for initial production batches should simulate production batches and should produce product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified.

6.3.2 Stability studies should be performed on each individual strength/concentration and container size of the cannabis product unless bracketing or matrixing is applied. Other supporting data can be provided.

TABLE 1 Suggested Analytical Tests for Cannabis Stability Testing

Analytical Test	Example Cannabis-Based Products					
	Flower	Extracts	Edibles	Topicals	Liquids	Suggested Technique
Sensory						
-appearance	X	X	X	X	X	Spectroscopy or Organoleptic
-odor	X	X	X	X	X	Olfactometry or Organoleptic
-clarity (phase separation			X	X	X	Light scattering or Organoleptic
Profile						
-cannabinoids	X	X	X	X	X	HPLC-UV or -DAD LC-MS/MS
-terpenes	X	X	X	X	X	HS-GC-FID or HS-GC-MS
Microbials						
-yeast and mold count	X	X	X	X	X	Plating
-aerobic plate count	X	X	X	X	X	Plating
-Shiga-toxin producing *E. coli*	X	X	X	X	X	qPCR or plating
-*Salmonella* spp.	X	X	X	X	X	qPCR or plating
-*Aspergillus* spp.						qPCR or plating
Mycotoxins	X	X	X	X	X	Immunochemistry or LC-MS/MS
Heavy Metals		X[A]				ICP-MS
Water Activity	X	X	X	X		Water activity meter or Karl-Fischer
Moisture Content	X					Analytical moisture balance

[A] Heavy metals analysis is recommended when primary container contains metal components.

6.4 *Container Closure System:*

6.4.1 Stability testing should be conducted on the product form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the cannabis product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the product form or can be considered as supporting information, respectively.

6.5 *Methods:*

6.5.1 Stability samples should be clearly labeled and stored separately from other sample lots to avoid potential mix-ups. Stability studies should include testing of those attributes of the cannabis product that are susceptible to change during storage and are likely to influence quality and safety. Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies. Examples of considerations for analytical methods and tests for comment cannabis products are provided in Table 1.

6.6 *Testing Frequency:*

6.6.1 For long term studies, frequency of testing should be sufficient to establish the stability profile of the cannabis product. For products with a proposed shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf-life (see Table 2).

6.6.2 At the accelerated storage condition, a minimum of three time points, including the initial and final time points (for example, 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

6.7 *Storage Conditions:*

6.7.1 In general, a cannabis product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

6.7.2 Stability testing of the cannabis product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product.

6.7.3 The long-term testing should cover a minimum of 12 months' duration on at least three initial production batches and should be continued for a period of time sufficient to cover the proposed shelf-life. Additional data accumulated during the assessment period should be submitted to the appropriate regulatory authorities if requested. Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping). Long term and accelerated storage conditions for cannabis products are detailed in Table 3. Alternative storage conditions can be used, if justified.

6.7.4 Shelf-life shall be determined based on successful stability of the product out to the desired expiration date or until the product fails to meet its specifications. Failure to meet the acceptance criteria for those analytes may depend on the intended use of the cannabis product.

6.8 *Evaluation:*

6.8.1 A systematic approach should be taken in the evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the product form.

6.8.2 The purpose of the stability study is to establish, based on testing a minimum of three batches of the cannabis product, shelf-life and label storage instructions applicable to all future batches of the cannabis product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

6.9 *Data Analysis:*

6.9.1 An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 % one-sided confidence-limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (for example, p-values for level of significance of rejection of more than 0.05) to the slopes of the regression lines and zero-time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

6.9.2 In general, certain quantitative chemical attributes (for example, assay, degradation products, preservative content) for a cannabis product can be assumed to follow zero-order kinetics during long-term storage. Data for these attributes are therefore amenable to linear regression analysis and probability testing. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis.

TABLE 2 Stability Testing Timepoints

NOTE 1—Manufacturers or independent testing labs should test each timepoint until the desired shelf-life is achieved.

Study Type	Time Zero	3 mos	6 mos	9 mos	12 mos	18 mos	24 mos
Long Term	X	X	X	X	X	X	X
Accelerated	X	X	X				